"Function and Dysfunction of Cysteine String Protein-a (CSPα): Not Just a Synaptic Chaperone"

Manu Sharma, Ph.D.
Assistant Professor of Neuroscience
Weill Cornell Medicine

Research Abstract
Our lab studies cellular mechanisms that maintain protein homeostasis in neurons, and how failures in proteostasis contribute to neurodegenerative diseases. Adult-onset neuronal ceroid lipofuscinosis (ANCL) is an invariably fatal lysosomal storage disease with no treatment and no known mechanism of pathogenesis. The project to be discussed is aimed at delineating the molecular mechanism of ANCL caused by mutations in Cysteine String Protein-α (CSPα). Recently, several independent studies have found ANCL-causing mutations in the gene encoding cysteine string protein-α (CSPα); yet, a gap persists in our understanding of exactly how ANCL mutations in CSPα lead to lysosomal dysfunction and neuron death. Previously, CSPα was shown to chaperone the synaptic SNARE protein SNAP-25 (Sharma et al. 2011). Now we have found that the SNAP-25 homolog SNAP-23 is also a client of the CSPα/Hsc70/SGT chaperone complex. Importantly, SNAP-23 is a SNARE protein which mediates lysosomal exocytosis, thus offering a direct connection from CSPα dysfunction to lysosomal pathology in ANCL. The presentation will be about progress in this ongoing project.

Recent Publications


Sharma M*, Burré J, Südhof TC*. Proteasome inhibition alleviates SNARE-Dependent neurodegeneration. Science Translational Medicine, 2012; 4(147):ra113. [*Corresponding authors; PMID: 22896677; PMCID: N/A]